Review Article

The Effects of Topical Application of Melatonin on Periodontal Disease in Diabetic Patients

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Abstract

Periodontal disease is a chronic disease, affects the supporting tissues of the tooth. The clinical manifestation varies from gingivitis to periodontitis. Periodontal disease is caused by bacterial infection that release toxins. The imbalance between oxidants and antioxidants determines the progression of periodontal disease. Melatonin (MEL), (N-acetyl-5-methoxytrittamine) is a hormone in the human body. Its production takes place in various organs including the retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes, skin, and principally pineal gland. Its main function is the regulation of the circadian and seasonal rhythm, body weight, reproduction, bone metabolism, and tumor growth. An important function of melatonin is the ability to reduce oxidative stress. The aim of this review is to evaluate the necessary effects on melatonin on the progression of periodontal disease and diabetes. The purpose of this review is to answer to the following questions using a PICO method (P: patient problem/population; I: intervention; C: comparison; O: outcome): (1) Can adding melatonin in diabetic and periodontal patients lead to improved periodontal health? (2) Does melatonin also affect the control of blood sugar levels in the diabetic patient? The study was conducted utilizing the main scientific databases (PubMed, MEDLINE, and WEB of SCIENCE). The time window considered for the electronic search was from March 1, 2007, to March 1, 2020. The following inclusion criterion was used: articles in English, human studies and clinical trials. Two independent people search with the same keywords all article and select the article founding. The risk of bias in this phase is solved by an independent author that conduct the same search. We can hypothesize that melatonin may indirectly help control blood sugar levels. Further studies will be needed to evaluate a direct healing effect of melatonin on diabetes.

Keywords: Diabetes, melatonin, periodontal disease

Introduction

Periodontal disease is a complex multifactorial condition whose clinical manifestation varies from the loss of the clinical attachment level in the periodontal structures to tooth loss. The bacterial infection is undoubtedly the reason for the pathology. In fact, bacteria invading periodontal tissues release toxins that create direct damage. Furthermore, another contributing factor is the host's own immune system. The molecular mechanisms and complete etiopathogenesis are not yet fully understood.[1] The host responds through the production of enzymes including alkaline phosphatase and acid phosphatase, these two intracellular enzymes are ubiquitous and are the main cause of bone resorption. According to several studies, periodontal disease causes an imbalance of some blood indices including hemoglobin A1c, fasting blood glucose, and inflammatory markers (such as interleukin-1 beta [IL-1β], tumor necrosis factor-alpha [TNF-α], and IL-6). Periodontitis has a correlation with other chronic inflamed conditions including atherosclerosis, cardiovascular disease, rheumatoid arthritis, and diabetes mellitus.[2] The mechanisms beneath this correlation are not yet clear, however, it is hypothesized that all these pathologies are linked by a chronic inflammatory state. Diabetes is an endocrine disorder that causes the systemic

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increase in inflammatory cytokines including IL-6, TNF-α, and IL-10. In fact, it has been noted that the presence of a state of systemic inflammation can promote diabetes. There is a relationship between periodontal disease and diabetes that by curing one of the two there can be an improvement in the other. All this happens because both pathologies cause a state of chronic systemic inflammation.[3] The improvement of systemic inflammation therefore leads to the improvement of inflammatory pathologies. In addition to bacterial toxins and the immune reaction, damage to the periodontal tissues is due to the generation of free radicals. The radical levels that create the damage are the reactive species of oxygen and nitrogen. An imbalance is therefore created with the increase in free radicals compared to antioxidants.[4] Melatonin is a derivative of indoleamine, it is mainly produced by pineal gland and its release follows a circadian rhythm. It has multiple functions including the control of the sleep-wake rhythm, the activation of the immune system and regulates the body temperature. Melatonin has an antioxidant effect and reduces the amount of free radicals. In addition, melatonin has important anti-inflammatory and bone repair effects. Melatonin is a lipophilic molecule and approximately 24%–33% of the plasma concentration manages to penetrate the salivary glands. It is easily measured in saliva using a radioimmunoassay.[5] The aim of the research is to evaluate whether the application of topical melatonin blocks the progression of periodontal disease. Therefore, melatonin can help improving periodontal indexes. In the articles examined, the change in periodontal indices after melatonin application was assessed. In addition, changes in both the saliva and blood of some inflammatory markers were evaluated.

Materials and Methods

The study was conducted utilizing the main scientific databases (PubMed, MEDLINE, and WEB of SCIENCE). The time window considered for the electronic search was from March 1, 2007, to March 1, 2020. The term "melatonin" was first combined with "periodontal disease" and then independently with "diabetes" using the connector "AND." The web search was assisted using MESH (Medical Subjects Headings). The criteria for this review are described in PRISMA flow diagram. The purpose of this review is to answer to the following questions using a PICO method (P: patient problem/population; I: intervention; C: comparison; O: outcome):

1. Can adding melatonin in diabetic and periodontal patients lead to improve periodontal health?
2. Does melatonin also affect the control of blood sugar levels in the diabetic patient?

The following inclusion criterion was used: articles in English, human studies and clinical trials. Two independent people search with the same keywords all article and select the article founding. The risk of bias in this phase is solved by an independent author that conduct the same search. The phase of screening is carried out by the two independent research that excluded the article duplicated, review and animal study. The article found in this phase is 50. 15 articles are excluded because are duplicates and they do not respect the topic proposed in this review.

The phase of eligibility is conducted by other two reviewers. These authors compare the article founding and select the article that asked the PICO. Articles which did not contain data regarding periodontal disease, melatonin, and salivary are excluded. The authors read first the abstract of all articles, excluded which did not respect the inclusion criteria, after read the complete test of the remains articles. In this phase, 26 articles are excluded.

In this phase, the risk of bias is solved by an independent author, completely external and unknown to the authors. The number of articles remaining in this phase is 9. Three article is excluded because did not use the periodontal index and treats only of oral health.

The synthesis of data is carried out by the authors. All data were extracted. The author reads first the abstract of all articles, after read the complete test of the articles. All the reviewers extract the data regarding the periodontal health, diabetes, and melatonin. Articles which not contain the data and the previous keywords were excluded. All doubts, regarding the included articles, are solved contacting the author [Table 1]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Two independent scientists searched the previously mentioned keywords, read the titles and summarized the abstracts of articles. During an initial reading, they excluded the articles that did not respect the topic. Therefore, articles that responded to the key characteristics were selected. These remaining articles were read and 4 of them were excluded because it did not conform to the inclusion criteria established. The complete text of the 6 remaining articles was read, and all were found to respect the inclusion criteria. In conclusion, 4 articles were included in the present review. The scientists extrapolated the following data: periodontal index, salivary concentration of bone markers, plasmatic concentration of bone markers, plasmatic concentration of inflammatory cytokines, salivary concentration of cytokines, number of patients, mean age, sex, salivary melatonin concentration, blood melatonin concentration, and melatonin crevicular concentration. Data comparing the concentration of melatonin between patients with periodontal disease and healthy controls were taken into account and extrapolated.

The Cutando study evaluated the change in the periodontal indexes (gingival index and pocket depth), of the markers

concentration of bone turn over in saliva. These markers are acid phosphatase, alkaline phosphatase, osteopontin, and osteocalcin. Thirty patients with diabetes and periodontal disease and 30 healthy controls were considered in the cross-sectional study. The 1% melatonin cream was applied once a day for 20 days to patients with diabetes and periodontal disease. The placebo group was administered to the control group. Quantitative variables are expressed as the mean ± standard deviation. The paired Student's *t*-test was used for the comparison of the gingival index and probing depth before and after topical application of melatonin among patients with periodontal diabetic disease, and the *t*-test for independent samples for the comparison of salivary levels of acid phosphatase, alkaline phosphatase, osteocalcin and osteopontin between the groups of diabetic patients and healthy controls.

Before the treatment, alkaline, acidic, and osteopontine phosphatase levels were higher in the group of diabetic and disease patients ($P < 0.01$). After 20 days of treatment, patients showed a statistically significant improvement in periodontal indices, specifically, the gingival index (15.84 ± 10.3 vs. 5.6 ± 5.1) and pocket depth (28.3 ± 19.5 vs. 11.9 ± 9.0) ($P < 0.001$) have changed. Bone biomarkers have all improved after melatonin treatment. It was noted that the decrease in acid phosphatase and osteopontin was related to the change in the gingival index, while the change in alkaline phosphatase was linked to the change in pocket depth.[6]

The Cutando study evaluated the levels of RANKL, osteoprotegerin (OPG) and melatonin after topical application of melatonin in patients with periodontal disease and diabetes. Thirty patients with diabetes and periodontal disease and 30 healthy controls were considered in this cross-sectional study. The concentrations of salivary RANKL and OPG and melatonin were measured in these two groups before and after topical application of melatonin. Diabetic 1% melatonin cream was applied once a day for 20 days. Diabetic patients have been treated with topical application of melatonin (1% orabase cream formula) once a day for 20 days, while the control group on a placebo. Before treatment, patients with diabetes showed higher RANKL and lower OPG levels than in the control group. Finally, they demonstrated a lower level of both salivary and plasma melatonin. After treatment, the periodontal parameters of patients with diabetes improved. Specifically, the gingival index (15.8 ± 10.26 vs. 5.6 ± 4.08) and pocket depth (28.3 ± 19.48 vs. 11.9 ± 9.01 mm) have improved. The salary levels of RANKL (102.6 ± 66.67 vs. 73.5 ± 47.39 pg/mL) ($P = 0.001$) also decreased, while those of OPG (10.4 ± 7.61 vs. 16.9 ± 7.20) ($P = 0.001$) increased. The changes in OPG are correlated with an improvement in the gingival index and pocket depth.[7]

The Cutando study evaluated the concentration variation of TNF-α, IL-6 and C-reactive protein (CRP) after topical application of melatonin. Thirty patients with periodontal disease and diabetes and 30 healthy controls were enrolled. Serum quantification of TNF-α and IL-6 and CRP was performed. The study group was treated with topical application of 1% melatonin once a day for 20 days. The control group was treated with placebo. Prior to treatment, patients with periodontal disease and diabetes had higher levels of TNF-α, IL-6 and CRP compared to healthy controls ($P < 0.001$). After topical application of melatonin, a decrease in gingival index and pocket depth was observed ($P < 0.001$). As regards serum markers, a decrease in IL-6 and CRP occurred ($P < 0.001$).[8]

Montero assented the effects of topical application of melatonin on the ILs in the crevicular fluid and on the periodontal indices (gingival index and pocket depth). The ILs taken into consideration are IL-1β, IL-6 and prostaglandin E2. Ninety patients were enrolled and divided into three groups. The first group consists of 30 patients with diabetes and periodontal disease who have been given melatonin. The

Table 1: Flow chart of the review process

Identification of articles	Papers identified through principal database (PUBMED, MEDLINE, WOS) *n*: 50
Screening time	After an initial read of titles and abstract *n*: 35
Eligibility	A full text reading and a check of inclusion or exclusion criteria *n*: 10
Included	Studies included *n*: 4

Table 2: Results of study

Study examined after PRISMA review (PUBMED, MEDLINE, WOS)	Type and structure of the study	Results
Cutando *et al*.[6]	Assessment of the change in concentration of acid phosphatase, osteopontin, osteocalcin, before and after application of topical melatonin	Improvement of periodontal condition
Cutando *et al*.[7]	Assessment of the change in concentration of RANKL, OPG and melatonin before and after application of topical melatonin	Improvement of periodontal condition
Cutando *et al*.[8]	Assessment of the change in concentration of TNF-α, IL-6 , CRP before and after application of topical melatonin	Improvement of periodontal condition
Montero *et al*.[9]	Assessment of the change in concentration of IL	Improvement of periodontal condition

TNF-α: Tumor necrosis factor-α, IL-6: Interleukin-6, CRP: C-reactive protein, OPG: Osteoprotegerin

second group consists of thirty patients with periodontal disease and diabetes who received a placebo. The third group is made up of 30 healthy people who received a placebo. The patients in the first group were treated with topical application of 1% melatonin once a day for 20 days. After the administration of melatonin, the patients of the first group showed a statistically significant improvement in the periodontal parameters. The gingival index and pocket depth change in this way 15.84 ± 10.26 vs. 5.59 ± 4.08, 2.8 ± 1.9 vs. 1.8 ± 1.2. In the first group, there were a significant decrease of IL-1β (127.73 ± 99.50 vs. 114.34 ± 74.88 ng/mL, $P = 0.012$), IL-6 (0.57 ± 0.07 vs. 0.47 ± 0.07 pg/mL, $P < 0.001$), and PGE2 (265.42 ± 101.60 vs. 222.78 ± 87.88 ng/mL, $P < 0.001$).

Instead, in the group of diabetic patients treated with placebo, there was no improvement in periodontal parameters.[9]

Conclusion

Periodontal disease is a chronic disease that causes destruction of the bone and periodontal ligament. The pathophysiology is not yet fully clarified. Obviously, bacteria are the main culprits of the pathology, causing direct tissue damage due to toxins. However, the host also contributes to damage periodontal structures through the production of inflammatory molecules including cytokines and prostanoids [Table 2]. Hence, we can say that the pathology is due both to a bacterial stimulus but also to an immune response of the host. In fact, in patients with periodontitis there is an increase in the serum concentration of proinflammatory cytokines and proinflammatory mediators, including ILs, such as IL-7, IL-6, IL-1β, TNF-α and CRP. In fact, the link between periodontal disease and other systemic diseases on an inflammatory basis is very close. In fact diabetes is a metabolic pathology that causes the increase of pro-inflammatory cytokines including IL-6, TNF-α, and IL-10.[10] Therefore, the link between these two pathologies is now very clear and they can influence each other. There are several molecules involved in periodontal disease. Recently, it has been observed that cyclooxygenase contributes to the production of E2 (PGE2). Other important mediators that stimulate the production of prostaglandins are IL-1β and IL-6. Therefore, in the presence of this molecule, human fibroblasts increase the production of cyclooxygenase-2 through the tyrosine kinase pathway. Therefore, the concentration of PGE2 in the crevicular fluid of patients with periodontal disease is higher than in healthy controls. In response to bacteria and cytokines, the body produces a series of intracellular enzymes.[11] The most important and probably those involved in periodontal disease are alkaline phosphatase and acid phosphatase. In fact, studies have shown an increase in the activity of these enzymes in patients with periodontal disease.[12] In fact, as can be seen in the study of Cutando *et al*.,[6] the measurement of salivary alkaline phosphatase concentration can help to diagnose the periodontal disease, since they measure bone turn-over. Therefore, the destruction of bone tissue leads to an increase in the crevicular fluid of bone proteins including telopeptides type I collagen, osteocalcin, osteonectin, osteopontin, and bone phosphoprotein. The interaction between family members of the TNF, the ligand receptor activator NF-jB (RANKL), RANK and OPG regulate bone turn over. The discovery of the OPG/RANKL/RANK system has been of great importance in the discovery of the pathogenesis of periodontal disease.[13] IL-1β is a powerful cytokine that regulates and amplifies bone absorption through the production of prostaglandins and the activation of lytic enzymes. IL-1 stimulates a series of events leading to the profusion of other inflammatory mediators including MAPK, AP-1, and NF-κB which produce IL-1β of IL-6, IL-8 PGE2, and MMP-1.[14] Oxidative stress is the cause of many metabolic pathologies including diabetes and periodontal disease. Therefore studies show that thanks to the use of melatonin an improvement of the periodontal situation can occur. Studies consider diabetic patients because there is a connection between diabetes and melatonin.[15,16] There are studies linking the synthesis of melatonin with that of β-insulin. Many studies have claimed that increased insulin causes inhibition of melatonin production.[17] Therefore, there is an antagonism between the two molecules. Several mechanisms by which insulin and melatonin interact have been hypothesized. Norepinephrine is the main neurotransmitter present in the pineal gland which stimulates the production of melatonin. Thanks to animal studies, norepinephrine levels in the pineal gland have decreased in diabetics.[18] Melatonin synthesis begins with tryptophan, but the absolute amount of tryptophan is reduced in the pineal glands of diabetic animals. Furthermore, glycemic alteration can lead to a lack of functionality of the enzymes that produce melatonin. All the studies analyzed affirm that the application of melatonin improves all the periodontal indexes and the inflammatory markers. Therefore, the improvement of periodontal health leads to a lower systemic inflammatory level and consequently a better control of the glycemic levels. However, although unclear, there are interactions between melatonin and diabetes. In fact, the improvement in blood glucose levels leads to an increase in melatonin production. However, further studies are needed to evaluate melatonin's efficacy directly on diabetes. One of the main effects of melatonin is the reduction of osteoclast activity and so reduces bone resorption. In addition, melatonin has osteoconductive effects. In fact, it helps the formation of scaffolds for bone regeneration, so much that it can be used in implantology to increase osseointegration. Furthermore, melatonin induces the differentiation from pluripotent cells of the bone marrow from preosteoblasts to osteoblasts. It also creates a reduction in the differentiation period of osteoblasts from 21 to 12 days.[19-32] In the studies analyzed, we can only come to the conclusion that the application of melatonin results in an improvement of the periodontal health. Therefore, given the strong link between diabetes and periodontal disease, we can hypothesize that melatonin may indirectly help control blood sugar levels. Further studies will be needed to evaluate a direct healing effect of melatonin on diabetes.

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Conflicts of interest

There are no conflicts of interest.

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